AMGEN

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Date: ▶ August 3, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: **Docket No. 2005D-0203**
Draft Guidance for Industry on Safety Testing of Drug Metabolites

Dear Sir/Madam:
Amgen is a leading human therapeutics company in the biotechnology industry based in Thousand Oaks, California. In general we agree with the intention of the draft guidance, *Safety Testing of Drug Metabolites,* and find it helpful. We are pleased to provide the following comments:

Lines 27-30: "*...defines major metabolites primarily as those identified in human plasma that account for greater than 10% of drug related material (administered dose or systemic exposure whichever is less) and that were not present at sufficient levels to permit adequate evaluation during standard nonclinical animal studies.*"

Comment: Text "*whichever is less*" needs clarification: Does it mean that if a metabolite is >10% of circulating drug-related material but <10% of excreted material, or vice versa, we do not have to test it?

Lines 148-152: "*Additionally, when a potentially clinically relevant toxicity is observed during standard nonclinical toxicity studies, it is prudent to determine if metabolites contribute to that finding. In such cases, we recommend that the metabolites be synthesized and directly administered to the appropriate animal species for further pharmacological/toxicological evaluation.*"

Comment: Because it is likely that for most drug candidates, toxicities will be identified that have some potential clinical relevance, the guidelines as currently written would inappropriately necessitate frequent studies to determine whether the metabolites played a role in that toxicity. Currently, the assumptions are that if the metabolites are present in the pre-clinical species, their role in the toxicity has been adequately addressed. We believe this practice to be sufficient, except for the special circumstance already described in the guidance.

Lines 182-184: " *We recommend consulting the ICH Q3A (ICH guidance for industry Q3A Impurities in New Drug Substances) guidance with regard to the development of analytical methods for measuring metabolites in selected matrices."*

Comment: The relevance of the reference to the point stated is not clear. ICH Q3A does not contain substantial information regarding "development of analytical methods for measuring metabolites in selected matrices."

Lines 210-215: *"It is important to consider combined exposure....."*

Comment: We suggest moving this paragraph to the *Introduction* section as it is general in nature and is not specific to *Study Design*.

Lines 235-237: *"An important objective is to identify dose-dependent toxicity. We recommend that the maximum dose either elicit frank toxicity without causing excessive incidence of morbidity/death or be the maximum feasible dose up to 2000 mg/kg/day."*

Comment: We suggest that for unique metabolites attempting to determine an MTD per se, or dosing to maximum feasibility is not necessary, is not scientifically justified, and is not consistent with what is described as acceptable for metabolite exposure elsewhere in this document. Our alternative suggestion is that the metabolite be dosed at a level that results in plasma exposure (AUC) approximately equivalent (on a molar basis) to the exposure of the parent compound achieved at its MTD, or up to a dose that is the MTD for the metabolite, whichever is less.

Lines 239-241: *"We also recommend using the intended clinical route of administration of the product..."*

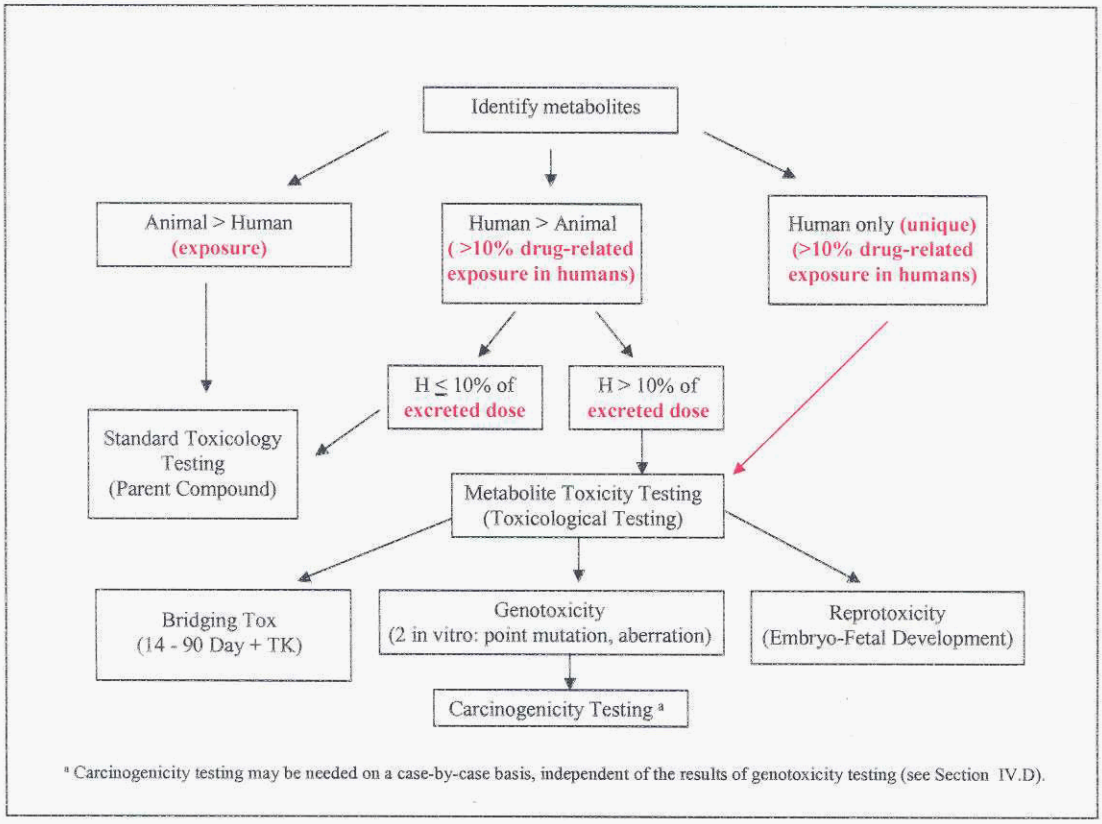
Comment: We suggest deleting the above sentence since the clinical route (typically oral) of delivery may not reflect the "route" of exposure to the endogenously formed metabolite. The route of administration needs to be determined on a case-by-case basis to achieve appropriate exposure.

Lines 286-290: *"If toxicity studies of a human metabolite are warranted, we recommend studies be completed and the study reports be submitted to the Agency before beginning large-scale phase 3 trials. In some cases, it may be appropriate for these nonclinical safety studies with unique human metabolites to be conducted before phase 3 studies; for example,..."*

Comment: With regard to the timing of safety assessments, the first sentence is not consistent with the second sentence. We suggest that there should be flexibility in timing of these studies depending on the data available from clinical and nonclinical studies. Hence, we suggest that it should not be mandatory to complete these studies before phase 3 initiation in all cases.

Line 352: *"Decision Tree Flow Diagram (Appendix A)"*

Comment: We suggest the following changes to accurately reflect the decision criteria in the draft guidance. Changes are below, in bolded, red text.



If you have any questions regarding our comments, or ideas how we may assist with further development of this guidance, please contact Jenny Peters at 805-447-8840.

Sincerely,

Jenny Peters
Amgen Regulatory Affairs